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A Systematic Review, Narrative Synthesis and Quantitative Comparison on Skin Penetration and Experimental Evidence of Metal and Metal oxide Nanoparticles in Cosmetic Related Applications

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ABSTRACT: Background. Metal and Metal oxide nanoparticles (NPs) (ZnO, TiO₂, Ag, Au, CeO₂, SiO₂, Al₂O₃) are used in sunscreens, anti ageing creams, antimicrobial cosmetics, oral care products. The evidence on whether they cross the skin barrier, how their safety and efficacy differ is scattered.

Objective. To find, summarise, and compare the experimental, clinical, and case study evidence on these NPs in cosmetic and dermal exposure contexts along with focusing the direct comparisons between the types of NPs.

Methods. From the PubMed and Scopus databases searched (finalised September 2026) using the nanoparticle specific and cosmetic/skin terms, following PRISMA 2020. The Records were screened in two stages. The eligible studies were primary research, clinical trials, or case studies. The Reviews and conference abstracts were excluded. Data for the quantitative synthesis were taken from the full texts where available. The Comparisons that included head to head experiments, dose/structure response within studies, cross study numeric comparisons, and evidence density mapping.

Results. From 953 records (150 - PubMed, 803 - Scopus), 39 studies were eligible (ZnO - 25, TiO₂ - 8, Ag - 5, Au - 4, SiO₂ - 1, CeO₂ - 1, Al₂O₃ - 0) in that 8 numeric comparisons were found. ZnO NPs showed stronger antibacterial activity than TiO₂ NPs, while TiO₂ NPs had slightly higher antioxidant activity. ZnO NPs penetration increased 60–65 fold in barrier impaired skin, while TiO₂ NPs deposition was similar in intact and damaged skin. SiO₂ NPs coating reduced ZnO NPs cytotoxicity across multiple endpoints. Ag NPs and ZnO NPs were positive for skin sensitisation, with size dependent potency for Ag NPs. TiO₂ NPs was used more often than Au NPs in marketed cosmetics products. The Co exposure of ZnO NPs and TiO₂ NPs produced antagonistic toxicity. CeO₂ NPs reduced the organophosphate penetration 3–4 fold in a barrier cream.

Conclusions. Evidence is concentrated on ZnO NPs and TiO₂ NPs, mostly In vitro and animal models. ZnO shows stronger barrier status dependence than TiO₂ NPs. Al₂O₃ NPs, SiO₂ NPs, and CeO₂ NPs are under studied. Direct experimental comparisons give the most reliable cross nanoparticle insights. A pooled meta analysis was not possible due to limited numeric data, and this is stated clearly.

1. INTRODUCTION

1.1. Skin Structural organisation, Aging, and Nano applications in Cosmetics

Human skin is the body's largest organ and its primary role that acts as a protective barrier against the external environment. The thickness of stratum corneum is about 15 – 20 μm and it composed of corneocytes embedded in a lipid matrix. This forming a brick-and-mortar structure that intentionally resistant to the penetration of foreign particles. Under this layer the viable epidermis and dermis contain the diverse types of cells that present including keratinocytes, fibroblasts, melanocytes and Langerhans cells along with a dense network of capillaries and nerves. This arrangements of the cells clearly says that any material penetration induce the genuine biological responses [1, 2].

As the skin ages, the production of collagen and elastin from the dermal cells are slows down that resulting in sagging and wrinkling formation. The majority of the conventional anti-ageing creams can only act on the superficial layer hence, the outcomes are short-term effects. This is the reason why new cosmetic products, involving the nanotechnology for try to drive the active ingredients deeper to the dermis where the actual ageing process occurs [3].

Nano cosmeceuticals are simply high-tech containers filled with active molecules, which are encapsulated in minute vesicles that including Nano emulsions, Nano capsules, liposomes, solid lipid nanoparticles, and dendrimers. The size ranges from 1 to 100 nm. These small carriers help to load the ingredients into the skin, maintain and deliver them to the areas where they are needed and mainly leaving the minimal residue on the skin's surface. With the advancements in nanotechnology, the jump from the formulations of olden days to formulation control of the products to reduce the environmental footprint and enhance the skin penetration. Nanocarriers with antioxidant properties are also considered for the innovations taken in the designing of the anti-ageing products [4]. This review focuses on the metal and metal oxide nanoparticles (NPs) used in the cosmetic applications. Here, the highly usable NPs in the cosmetic industries are selected and discussed.

1.2. The Importance of Metal and Metal oxide NPs in Cosmetic formulations.

Based on the literature review and the current regulatory discussion, seven classes of metal- and metal-oxide NPs are identified and the ongoing debate around nanotechnology in cosmetics: Zinc oxide (ZnO), Titanium dioxide (TiO_2), Silver (Ag), Gold (Au), Cerium oxide (CeO_2), Silica (SiO_2), and Aluminum oxide (Al_2O_3). ZnO and TiO_2 NPs are the primary inorganic UV filters in broad spectrum sunscreens [5, 6]. Ag NPs has a broad spectrum of antimicrobial activity that is used in acne, deodorant and wound related cosmetic products [7]. Au NPs is mainly used in high end anti-ageing and antifading products and in combination with other activities as a carrier [8]. CeO_2 NPs act as antioxidant and barrier protection agent, SiO_2 NPs act as an opacifying/texturising excipient as well as a coating shell for other metal oxide cores and also used for the membrane damage of bacteria [9]. Al_2O_3 NPs used as an abrasive/opacifying agent in few product formulations.

Each type of NPs has a role in cosmetic formulations because of their different physicochemical properties. The semiconductor properties like materials such as ZnO and TiO_2 NPs are responsible for their function as UV filters [10]. Ag NPs and Au NPs (lesser extent) have its functional roles as surface ion release and catalytic/plasmonic behaviour [11, 12]. CeO_2 NPs used in the reversible $\text{Ce}^{3+}/\text{Ce}^{4+}$ redox couple which is known for its free radical scavenging ability. On the other hand, SiO_2 NPs and Al_2O_3 NPs used mostly based on their surface area, porosity, and physical or optical characteristics, but not based on their reactivity.

1.3. Regulatory framework to cosmetic nanomaterials.

The regulation for NPs in the cosmetic products has been increased in the last 10 years. The European Union's Cosmetic Regulation (EC) No. 1223/2009 sets out the conditions for all the products which contain Nanomaterials to be notified to European Commission and labelled as with the suffix "nano" in their ingredients list. As ultraviolet (UV) filters, both ZnO and TiO_2 NPs have received a positive list of authorisations, which outlines the acceptable ranges of particle sizes, coatings and photostability conditions. Among the several forms of TiO_2 NPs can be inhaled, so mainly highlighted because it was classified as a substance that suspected to induce carcinogenicity by inhalation. This classification is mostly for occupational and respiratory exposures, but it also had implications on the public awareness and debate of dermal exposure, such as in the sunscreen formulations [13].

1.4. Purpose and Objectives of this Review

The reported narrative reviews of Metal and Metal-oxide NPs in cosmetics have generally taken in two ways. One either they have been generally to provide the qualitative information without following any methodology, or specifically providing the

toxicological information on individual NPs but not as comparison information analyzed under equivalent experimental conditions. When systematic search methodologies have been used, the publications of synthesis have been frequently limited to bibliographic level.

This review addresses the gap that identified through a reproducible, PRISMA 2020 applied systematic search from the two-source database screening (PubMed and SCOPUS databases). These sources used for the comprehensive narrative synthesis of primary and background literature, that organized by the types of NPs, attention for the cosmetic applications, NPs physicochemical properties and their dermatological related evidences. It further defines the mechanistic applications of NPs in Skin interactions and cellular toxicity. It also assessing the main methodological contribution through extraction and quantitative comparison of numerical findings from various studies across multiple NPs type under matched conditions. Each comparison that presented in comparative pictures and structured evidence-density map across various NPs type and their results. This literature review, which summarized the dermal exposure literature, forms the body of evidence that most relevant to the cosmetic risk assessment in the context of this regulatory environment. The difference is important, because of their safety profile for NPs in cosmetics should be assessed specifically with regard to dermal exposure. The routes of exposure and endpoints of exposure are very different from the occupational and inhalational routes.

2. METHODS

2.1. Protocol

This review was carried out through following the PRISMA 2020 guidelines that include systematic search, screening and flow diagram reporting. The synthesis does not report a single pooled magnitude of effect for the wide variety of outcomes. Instead, it combines head-to-head experimental comparisons with a structured evidence-density map. So, this review is clearly identified as a systematic review with a narrative synthesis and a quantitative (comparative and non-pooled) analysis.

2.2. Eligibility Criteria

A PICOS (Population-Intervention / Exposure-Curriculum-Outcome-Study design) adapted framework was used to determine the eligibility of the sources.

Population: The Seven different Metal and Metal – oxide NPs (ZnO, TiO₂, Ag, Au, CeO₂, SiO₂, Al₂O₃), which were studied in cosmetic, dermal exposure or skin relevant experimental contexts.

Comparator: They were compared in the classes of untreated or vehicle controls, bulk (non-nano) counterparts, to other types of NPs, or to a standard agent.

Outcomes: The Skin or tissue penetration and deposition, cellular or systemic toxicity, antimicrobial or antioxidant activity, sensitisation/immune response, and the product level detection or quantification.

Study design: The Primary research articles (In vitro, Ex vivo, animal or human), clinical trials and case studies were selected for the study design. Some of the review papers that not have the quantitative or comparative synthesis are only retained for the introduction and background literature part of this review.

Exclusion: Reviews, editorials, conference papers without peer-reviewed data, book chapters and records that not relevant to the field of cosmetic or skin were excluded.

2.3. Search Strategy and Search Databases

On **September 2026**, searches were conducted in **PubMed** and **Scopus** using keyword combinations of “ZnO”, “TiO₂”, “Al₂O₃”, “SiO₂”, “CeO₂”, “Au” and “Ag” NPs and with the terms “Cosmetics”, “Skin Penetration” (Table 1). Database-specific field restrictions were applied in the databases in Scopus, queries were limited (Title, Abstract, and Keyword) whereas in PubMed, searches were limited to (Title/Abstract) field.

Table 1: The Search strategy (keyword combination) used to obtain records from the different databases.

S.No.	Keywords (Search term combinations)	No. of Records from the certain databases	
		PubMed	Scopus
1	ZnO NPs and Cosmetics	78	270
2	TiO ₂ NPs and Cosmetics	30	206
3	Al ₂ O ₃ NPs and Cosmetics	1	14
4	CeO ₂ NPs and Cosmetics	3	20
5	SiO ₂ NPs and Cosmetics	2	39
6	Au NPs and Cosmetics	9	46
7	Ag NPs and Cosmetics	21	109
8	ZnO NPs and Skin Penetration	4	34
9	TiO ₂ NPs and Skin Penetration	1	25
10	Al ₂ O ₃ NPs and Skin Penetration	-	2
11	CeO ₂ NPs and Skin Penetration	-	3
12	SiO ₂ NPs and Skin Penetration	-	5
13	Au NPs and Skin Penetration	-	11
14	Ag NPs and Skin Penetration	1	19
Total = 953		150	803

2.4. Selection Process

The Records from the PubMed and Scopus were merged and de-duplicated from that 305 duplicate records were removed. After that obtaining 648 unique records to be screened in their title and abstract basis. In those 600 records excluded during this stage because they lacked the information that related to the skin or cosmetic applications, the 48 records were successfully retrieved. Of these, 9 did not meet the inclusion criteria during their assessment of full record. The final number of primary research articles and clinical/case studies eligible for inclusion was 39. Screening and eligibility assessment was performed against pre-specified criteria that mentioned in Section 2.2.

2.5. Data Extraction

The Data were extracted from each of the 39 studies included with respect to type(s) of nanoparticles and to any comparators like model of the studies (In vitro/cell-based, animal/Ex vivo, human/clinical), route and vehicle of exposure, as well as the domains of outcomes that measured. Importantly, numeric results in the study (means, standard deviations, sample concentrations, effective concentrations, and inhibitory concentrations, and percentage changes compared to controls), in addition to qualitative conclusions. In those 11 studies provided the direct data for 8 quantitative comparative synthesis reported in Section 6 as numeric outcome data such as a concentration (e.g., in µg/mL) or a percentage viability, but not just a directional comparative effect. The numeric values in Section 6 that not randomly interrupted, estimated, or any back-calculation, done only noted unit conversions (e.g., molar-to-mass conversion of TiO₂ in Section 6.5).

2.6. Outcome Domains

A narrative synthesis (Section 4) and evidence-density mapping (Section 6.11) were conducted using the six following outcome domains: (i) skin / tissue penetration or deposition under intact barrier conditions, (ii) skin / tissue penetration or deposition under barrier-impaired, UV-co-exposed or otherwise compromised conditions, (iii) In vitro cellular cytotoxicity, (iv) antimicrobial efficacy, (v) antioxidant activity and (vi) sensitisation or immune response.

2.7. Synthesis Methods

The review utilizes two alternative methods of synthesis.

Narrative synthesis: The primary literature and background reviews (references 1–13) used only for framing and mechanistic insight included in this review are arranged in a narrative synthesis (Section 4) that organized by types of NPs.

Quantitative synthesis: In quantitative synthesis (Section 6), only the numeric data (e.g., concentrations, percentages, effective/inhibitory values, fluorescence intensities) from primary source studies are used, not as the qualitative conclusions. Three types of numeric comparison are reported and clearly differentiated across:

a) **Matched head-to-head comparisons:** Studies comparing two or more types of NPs (or comparing NP against defined comparator) in the conditions of identical formulations, cell line / model and some other assays. These are represented as the most internally valid quantitative comparisons in this review (Sections 6.2–6.3, 6.6–6.7).

b) **Matched multi-arm dose- or condition-response comparisons:** Studies reporting the full numeric series across different concentrations, exposure duration or engineered variants (surface-coating) for the same NPs that providing a dose or structure response relationships (Section 6.6). Thus gives a comparison across these dose or structure response relationships rather than single point comparison.

c) **Functionally similar cross study comparisons:** Independent studies that similar in methodology (e.g., Ex vivo human skin Franz cell assays) have directly compared in their reported numeric outcomes, with the non-matched nature of the comparison explicitly stated (Sections 6.4 – 6.5b).

These are complemented by a structured evidence-density map (Figure 11.) that shows the distribution of each type of NPs across the various evidences and outcome domain, but does not suggest the direction or magnitudes for comparisons. A formal collective meta-analysis using random-effect sizes, forest plots and heterogeneity statistics was not performed. Due to the methodological heterogeneity across various studies which was not applicable statistically.

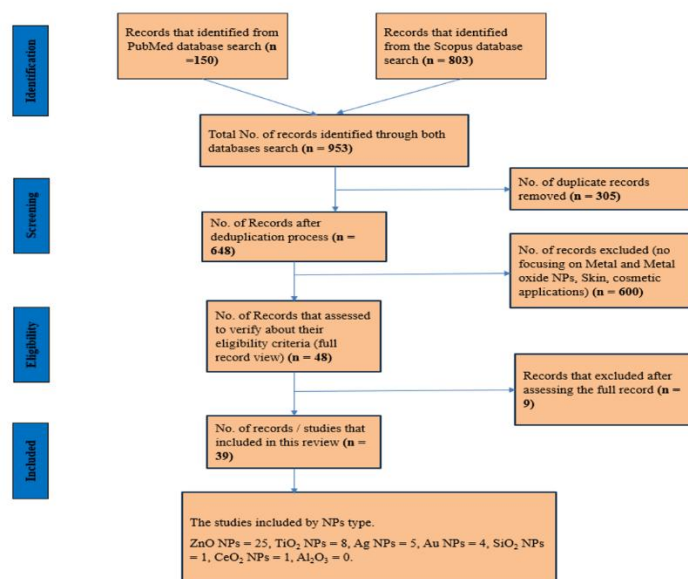
2.8. Risk of bias

A formal risk-of-bias scoring tool was not used as usual for record this review. As a transparency indicator, the included records providing a numeric value of the studies that related to the selected domain experiments / applications were monitored (in addition to Section 6). The full text validation should be performed before use of these values in cases where they are included.

3. RESULTS

3.1. PRISMA Flow diagram

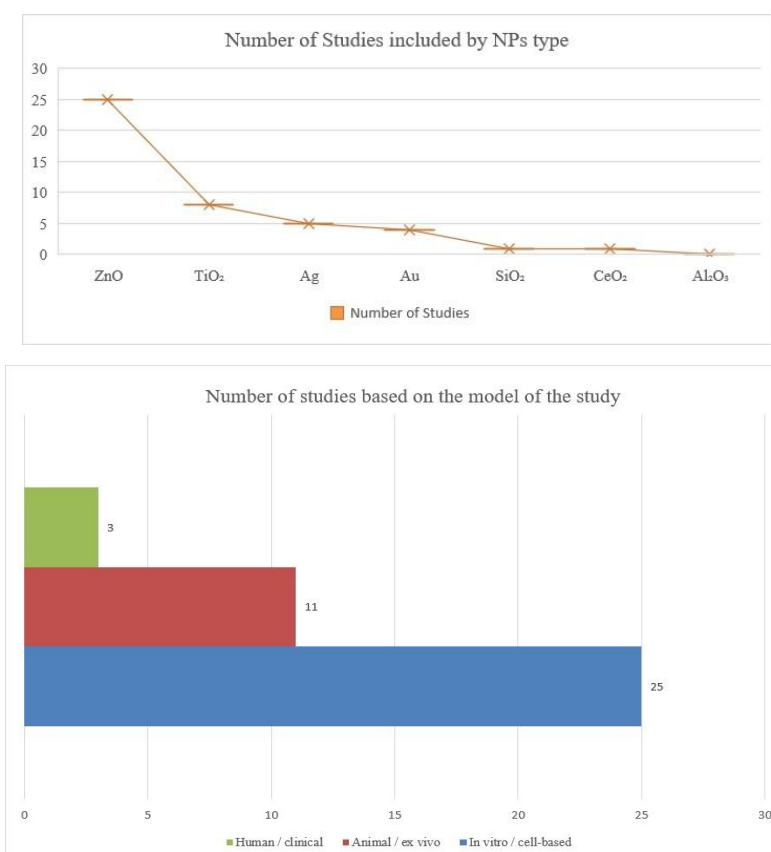
Figure 1: PRISMA Flow diagram



3.2. Characteristics of Included studies

The distribution of included studies mainly relies on ZnO NPs (25 of 39) and TiO₂ NPs (8 of 39) due to their action as a potent UV filter in the sunscreen formulations. Several reports assessed more than one type of NPs, so the type of level counts that more than the total number of included studies. According to the type of study model, the In vitro / cell-based studies (25 of 39) dominated followed that the animal / Ex vivo based studies (11 of 39) and human / clinical studies (3 of 39) had characterized.

Figure 2. a) The Number of studies included by NPs type in the study b) The Number of studies based on the study model.



4. NARRATIVE SYTHESIS: Types of NPs in Cosmetics or Skin related studies

Table 4. The usage of NPs in the cosmetic products.

Name of the Nanoparticle	Physicochemical aspects of NPs	Functional role of NPs used in Cosmetic products	Cosmetic products
Zinc oxide (ZnO)	Wide-bandgap (3.37 eV) semiconductor, easily dissolves to release Zn ²⁺ at acidic pH	UV filter, antimicrobial, Astringent	Sunscreens, creams, anti-acne, baby-care products

Titanium Dioxide (TiO ₂)	Wide-bandgap (3.0–3.2 eV) semiconductor, having anatase or rutile crystal phase	UV filter, opacifier/whitener	Sunscreens, and colour cosmetics products, toothpaste
Silver (Ag)	Noble metal, releases Ag ⁺ ions, strong plasmon resonance	Broad-spectrum antimicrobial/anti odour	Antimicrobial creams, deodorants, wound-adjacent cosmetics
Gold (Au)	Noble metal that has chemically inert core and tunable plasmon resonance	Delivery vehicle, antioxidant/anti-inflammatory claims	Premium anti-ageing serums, 'antifading' formulations
Cerium Dioxide (CeO ₂)	Reversible Ce ³⁺ /Ce ⁴⁺ redox couple reaction that responsible for oxygen-vacancy catalysis	Free-radical scavenging; catalytic detoxification	Emerging antioxidant/barrier-protectant formulations
Silica Dioxide (SiO ₂)	Amorphous and high surface area, inert core, and also used as coating shell	Oil absorption, carrier/coating, toxicity moderation	Mattifying powders, texturisers, NP surface coatings
Aluminium oxide (Al ₂ O ₃)	Hard, chemically inert ceramic oxide form of material	Mechanical exfoliation, opacity/whitening	Abrasive/exfoliant and opacifying agents (smaller share)

4.1. Zinc Oxide NPs

The most common NPs type in the included primary literature (25/39) was Zinc Oxide (ZnO) NPs. The significance of its usage due to its long history as a wide-range of potent UV filter, and some of toxicological studies that undergone. In Industries the synthesis of ZnO NPs is usually carried out by sol-gel, precipitation or hydrothermal techniques. More recently, by using green biosynthesis method for the synthesis of ZnO NPs, it has less toxicity [14]. In sunscreen products, ZnO NPs typically incorporated within the range of 40 to 200 nm, and combined with silica, alumina or silicone as a coating, to minimize its photocatalytic activity and enhance its cosmetic properties.

The Human and Ex vivo related experiments result for the ZnO NPs that meets the barrier-status-dependent penetration pattern. The ZnO NPs – Sunscreen products applied to the human volunteers repeatedly for five days. From the experiment results that the NPs penetrate beyond the Stratum corneum and associated in the cellular toxicity of viable epidermis [15]. The topical applications of sunscreen formulations containing ZnO NPs to the intact human skin that resulting as increasing the concentration of ZnO NPs in the epidermal region of skin. These experiments give a consistent result that the penetration in the minimal range (penetrate in outer epidermal region) and no penetration in deep dermal portions. [16, 17, 18]. The ZnO NPs penetration experiment demonstrated in Ex vivo human skin model that merely depend on barrier integrity. From that the ZnO NPs-Sunscreen formulations penetration has done on stratum corneum when it impaired. The ZnO NPs level in the viable epidermis is increasing sharply based on the dose and time dependent manner. After 24 hours and 48 hours the levels were 60 – 65-fold and 100-fold times increased respectively [17]. A quantitative comparison done along with the equivalent of TiO₂ NP evidences that shown in the figure 5 (section 6.4).

The UV-B co-exposure increases the ZnO NPs penetration and induces the inflammatory signaling through the activation of MAPK/NF- κ B pathway in hairless mice [19]. The Exposure of ZnO NPs on the skin that delaying the recovery of psoriasis-like lesions by NF- κ B translocation and cysteine depletion [20]. The prolonged exposure of ZnO NPs on the skin of barrier-deficient mice that resulted in the formation of melanoma-like lesions through dendritic-cell activation and adherence [21].

At the cellular level insights, the ZnO NPs have been reported that responsible for causing DNA damage in epidermal cells [22], induce p53/ p38-mediated apoptosis in fibroblasts [23], triggers ROS-ERK-Egr-1- signaling to induce activation of TNF- α [24] and cause impairment in autophagy through the activation of TRIM16-NRF2-p62 pathway in keratinocytes [25]. The Systemic exposure of ZnO NPs has been reported in renal cells that disrupts the lysosomal TRPML1-mediated autophagy. The systemic and reproductive toxicity signaling effects that related to including the plasma metabolomic changes, associated with hepatic steatosis [26] and altered in the level of monoaminergic neurotransmitters following the prenatal exposure in mice [27].

There are several parallel works looking for the usage of ZnO NPs as dermal delivery vehicles. The methods involved that using the ZnO NPs as a chemical-enhancer-modulated transdermal delivery [28], green synthesised ZnO NPs gels (hydrogel, oleogel, bigel) for enhancement of the dermal delivery [29] and preparation of berberine (BBR)-ZnO NPs for In vitro transdermal

permeation studies [30]. The new methodological developments that comprise a fibrin-hydrogel bioassay for assessing the zinc-induced changes in permeability and inflammation [31] and validated TOF-SIMS/CLSM imaging for the assessment of cytotoxicity in HaCaT keratinocytes [32]. The toxicological review of ZnO/TiO₂ NPs in the sunscreens indicates [5, 6] that are actually well tolerated by immune cells and also act as similar to the organic UV filters [33]. The murine chloroquine induced pruritus model studies indicate that the behaviour was similar between commercial and green-synthesised ZnO NPs [34].

4.2. Titanium dioxide NPs

The second most common type was Titanium dioxide (TiO₂) NPs (8 out of 39 studies). It is used together with ZnO NPs to provide the inorganic form of chemistry for cosmetic sunscreen (in the form of anatase / rutile / mixed phase) at particle sizes that comparable to cosmetic ZnO NPs. TiO₂ NPs are not soluble at physiological pH, so its dermal related behaviour not depends on ion release, but influence the transport of the particles and the surface photochemistry.

TiO₂ NPs penetration was assessed through Franz-diffusion-cell methodology by comparing the intact and needle damaged human skin. The concentration of TiO₂ NPs after 24 hours in the intact human skin and needle-damaged skin was $0.47 \pm 0.33 \mu\text{g}/\text{cm}^2$ and $0.53 \pm 0.26 \mu\text{g}/\text{cm}^2$ respectively. [35]. These are approximately in the range of similar in size, but their different order of magnitude significantly increases seen in ZnO NPs that quantitatively compared (section 6.4). Mixed anatase/rutile TiO₂ NPs having the capacity to induce oxidative damage through band-alignment under sunlight conditions, which is greater than the pure-phase particles [36]. The cellular origin of TiO₂ NPs-induced toxicity has been traced when the surface enhancement through spectroscopic techniques [37]. TiO₂ - Nanosheets have been found to be phototoxic and cytotoxic in a 3D reconstructed human skin model [38].

In typical formulations of sunscreen, including co-exposure of ZnO NPs and TiO₂ NPs, their toxic effects do not add instead they counter attack each other. TiO₂ NPs inhibited the cellular uptake of ZnO NPs to protect the keratinocytes and reconstructed human epidermis from ZnO NPs induced growth inhibition and DNA damage [39] (Section 6.8). Green synthesized ZnO NPs and TiO₂ NPs from the *Calotropis procera* leaf extract demonstrated complementary bioactivities. The ZnO NPs exhibited greater antibacterial activity and cytotoxicity while TiO₂ exhibited slightly higher antioxidant activity. Together they showed the synergistic antibacterial and cytotoxic effects (Sections 6.2-6.3) thus, highlights the potential of dual-NPs formulations in the applications of biomedical field [14]. The protein adsorption studies showed that BSA binding influences and significantly increase the cellular uptake of TiO₂ NPs into skin cells [40]. The presence of TiO₂ NPs in the cosmetic products confirmed through the elemental screening that more prevalent than the Au NPs (Section 6.7) [41].

4.3. Silver NPs

The role of silver (Ag) NPs in cosmetics is totally different than the role of ZnO NPs and TiO₂ NPs. The Ag NPs added to the various products due to its broad-spectrum antimicrobial activity which results from the release of Ag⁺ ions lead to oxidative and membrane-disruptive action [7]. The products which contain Ag NPs are in the form of antimicrobial cream, deodorants and cosmetic products for wounds. Fluorescence lifetime imaging microscopy, Raman microscopy and surface-enhanced Raman scattering microscopy was used for the visualization and imaging of Ag NPs penetration in the Ex vivo porcine Skin models [42]. The effect of NPs different according to their morphology (sphere, rod, plate and related shapes) the demonstrations done on antimicrobial efficacy, HaCaT keratinocyte cytotoxicity and skin deposition (even done in the burn wound relevant skin models) [43]. This illustrates the importance of Ag NPs that can be many different materials by varying their coatings and shapes also have different biological behaviours [12]. The biocompatibility of Ag NPs and that incorporated as biodegradable scaffolds has been confirmed in applications of skin-tissue engineering [44]. The synthesis of silver chloride NPs (AgCl NPs) through green synthesis method from *Bacillus megaterium*. These NPs modulate the Cytokine secretion (IL-6, IL-8, IL-1 β , IL-10) in human adipose stem cell spheroids at the sub-lethal dosage (5-25 $\mu\text{g}/\text{ml}$) application that relevant to the cosmetic or implant exposure [45]. Both Ag NPs and ZnO NPs were having the potential of skin sensitisation test through human cell-line activation test (h-CLAT) and included as agents in dermal-safety screening series [46] (Section 6.8).

4.4. Gold NPs

The Gold (Au) NPs used as favour of materials for delivery applications than dermal toxicology because of their relative chemical inertness. However, it is used in cosmetic formulations, which referred as anti-ageing, antifading agent and marketed as potent antioxidant and anti-inflammatory component. The co-administration of protein drugs with Au NPs was used as a strategy to perform the percutaneous delivery of skin penetration approach [47]. The type of reducing agent (Sodium citrate) was used in

synthesis and demonstrated to determine the Au-NPs physicochemical properties and its integration into hyaluronic-acid hydrogels. From the Onion extract, the synthesis of Au NPs having more stable particles with potent anti-oxidant activity. Both synthesis route of Au NPs successfully integrates with hyaluronic acid hydrogels, which have applications in cosmetics and biomedical fields [48]. An In-situ hydrogen-generation system was designed to using Au NPs as nano-photocatalysts to reduce the senescence-associated inflammation and skin ageing [49].

The Au NPs were very rarely found in commercial cosmetics products when compared to TiO₂ NPs in the sampled process categories [41] (Section 6.7). An overview of the well-documented applications of Au NPs, typically in combination with chitosan, in cosmetic and medicine applications [8] and highlight about the intracellular transport pathways that common in the Ag NPs [11].

4.5. Cerium Oxide NPs

A single primary study was identified in the applied search strategy, which reflecting the status of the usage of Cerium Oxide (CeO₂) NPs in cosmetic formulations. The applications of topical formulation of CeO₂ NPs for protection of skin against the exposure of organophosphate. The reversible Ce³⁺/Ce⁴⁺ redox cycle of nanoceria, which allowed for free-radical scavenging and catalytic neutralisation. The exposure of organophosphate to the skin (silicone membrane skin surrogate models) can be reduced 3- 4-fold times by CeO₂ NPs that incorporated into Oil-in-Water emulsion or fluorinated thickener suspension than the same formulation without CeO₂ NPs. This can be measured by using Franz diffusion cells method [50] (section 6.10). Although this one study evidence base is not enough to conclude as a general cosmetic safety profile for CeO₂ NPs. Their protective effect evidences are completely different from the UV-filtering effect of ZnO/TiO₂ NPs and the antimicrobial effect of Ag NPs. This is an actual evidence gap, and an opportunity to support further primary research (Section 7).

4.6. Silicon dioxide NPs (Silica NPs)

In cosmetic nanotechnology, silica has a distinctive position. It has dual function as a standalone mattifying or texturizing agent and also as a surface coating agent (ZnO NPs and TiO₂ NPs surface can be coated with SiO₂ NPs to reduce their photocatalytic activity and ion release). The only one eligible study that included in this review (quantitative comparison) that related to the coating effects.

The cytotoxicity effect was progressively reduced with human dermal fibroblasts by increasing the thickness of the Silicon dioxide (SiO₂) NPs shell on the surface of the ZnO NPs. The coatings with higher thickness SiO₂/ZnO NPs that resulted in lower rate of enzyme leakage, generation of ROS, and oxidative stress than other strength coatings like bare ZnO NPs or thin coating. This restricts the free radical formation and Zn²⁺ ion release from the core coated core [51]. This finding shows that the surface engineering is more important than NPs identity as one of the first order determinants of safety in cosmetic nanotechnology (see Section 5.2). The background literature about the silica specific membrane damage thresholds provides the additional mechanistic context for the uncoated SiO₂ NPs usage [9].

4.7. Aluminium oxide NPs

According to the applied search strategy, no eligible primary study was retrieved for Aluminium oxide (Al₂O₃) NPs (Figure 1). Al₂O₃ NPs is found in a smaller number of cosmetic products as an abrasive/exfoliating agent and also as an opacifier. The lack of the eligible studies should be show that there is a true lack of research, rather than as proof of non-use of cosmetics or as inferred evidence of safety or risk. This gap is not hidden in the evidence-density map (Figure 9, Section 6.11), but is clearly represented as a gap.

4.8. The types of synthesis method and their relevance to the comparative evidence basis

In Sections 4.1–4.6, the majority of the studies used in this Review are based on green or biosynthesised NPs (produced by a reduction process mediated by the plant-extract or microorganisms), in combination with other conventional NPs (Sol-gel, precipitation, hydrothermal, physical vapour) synthesis methods. Several head-to-head comparisons (e.g., antibacterial and antioxidant activity of green-synthesised NPs of ZnO NPs vs. TiO₂ NPs, Sections 6.2–6.3) are made with regard to green-synthesised NPs. The synthesis method can affect the particle size distribution, surface capping chemistry and biological reactivity, so that results cannot be extrapolated from one synthesis method to another. To avoid the misinterpretation beyond the tested material, the route of synthesis for each comparison has been clearly stated.

5. MECHANISM OF NPS – SKIN INTERACTION

5.1. Skin barrier structure and Types of penetration routes

Human skin consists of three layers: the top layer is the epidermis, followed by the dermis, and the deepest layer, the hypodermis (also referred to as the subcutaneous layer). The barrier component is the epidermis, which is interlaced with the keratinocytes and melanocytes, amongst other types of cells that all have their own stratum. Collagen and elastin fibres fill the dermis and provide the skin with the necessary elasticity and strength. However, as we age, the fibres become thinner, resulting in the other time-tested effects of wrinkles and sagging. In the meantime, the hypodermis is simply a lump of fat that insulates us and shields the underlying strata [1,2].

There are three anatomical routes for the penetration of NPs. They are i) Transcellular route (directly through the corneocytes), ii) Intercellular route (through hair follicle openings and lipid matrix between corneocytes) and iii) Follicular / Appendageal route (through hair follicle openings and associated sebaceous gland ducts which present as locally thinner and more direct pathway toward the viable epidermis and dermal vasculature). Across the included literature or studies mainly focusing the intercellular routes or follicular / appendageal routes that most implicated for the size range of cosmetic metal / metal oxide NPs. The Transcellular pathway does not focus majorly due to their rich corneocyte responsible for the resistance under the intact barrier conditions. This structural resistance can be clearly explained (ZnO NPs and TiO₂ NPs) in the Section 4.1 and 4.2.

5.2. Physicochemical properties that determine the penetration and reactivity

Across the various included studies and their evidence basis, the NPs behaviour was not only relied by chemical properties that also influences by their physicochemical properties.

- **Particle size and Aggregation state**

Smaller particle size and lower aggregation were favouring the greater follicular and intercellular routes of penetration. However, the most cosmetic-grade metal-oxide NPs aggregated substantially in the formulation that limiting the proportion of true nanoscale of the material presented to the skin surface.

- **Surface coating**

The Functional coatings (silane, silica, alumina, or organic agents such as PEG or citrate) measurably influence the both penetration and cytotoxicity of NPs. This directly demonstrated by the thickness-dependent reduction in ZnO NPs-core cytotoxicity achieved with a SiO₂ NPs shell [51], and boomed by BSA-adsorption-dependent modulation of TiO₂ NPs in cellular uptake [40].

- **Solubility and dissolution behaviour**

ZnO NPs comparatively having high dissolution rate to Zn²⁺ at skin-surface pH that mechanistically contrasted with TiO₂ NPs (insoluble). This mechanistic distinction reasonably highlights the sharper barrier-status dependence observed for ZnO NPs penetration relative to TiO₂ NPs in matched comparisons (Section 6.4). The soluble ions can diffuse through transport mechanism (aqueous diffusion) following dissolution, whereas the insoluble particles cannot have such kind of mechanism.

- **Crystal phase and photoactivity (semiconductor oxides)**

For TiO₂ NPs, anatase / rutile phases differed in their bandgap and photocatalytic reactivity. The Mixed-phase material produced greater band-alignment that driven oxidative skin injury under sunlight exposure than pure-phase particles [36]. This variability in their crystal composition parallels the shape-dependent reactivity (for Ag NPs) [43].

5.3. Mechanisms for the induction of cellular toxicity

From the included studies the insight of cellular and molecular basis action of NPs have been categorized into four kinds of mechanism that overlapping to one another.

- **Reactive Oxygen Species (ROS) generation**

The Photocatalytic (ZnO NPs, TiO₂ NPs) or Ion-catalysed redox chemistry (Ag NPs or protective manner of CeO₂ NPs) responsible for the production of ROS by lipid peroxidation, protein oxidation and oxidative DNA damage.

- **Ion dissolution and Release**

From the ZnO NPs (Zn^{2+}) and Ag NPs (Ag^+) the ions were released leads to the accumulation of toxic material (physiologically active form - Zn^{2+}) rather than the intact particle.

- **Direct membrane and organelle interaction**

The ZnO NPs studies show that it can block normal autophagy in keratinocytes through the inhibit the activation of TRIM16–NRF2–p62 pathway [25]. The same ZnO NPs can trigger autophagic cell death in renal cells through activation of TRPML1 signaling [52]. On the other hand, TiO_2 NPs affects mitochondrial function and membrane stability, which is reflected in the different EC_{50} values reported across cytotoxicity assays (Section 6.5).

- **Activation of Inflammatory signaling**

The activation of MAPK / NF- κ B mediated responses by the UV-B co exposure along with ZnO NPs [19], NF- κ B – p65 mediated effects in psoriasis like lesions [20] and TNF- α induction through ROS-ERK-Egr-1 signaling [24]. These indicating the cellular toxicity results for these NPs that frequently coupled or rather than the separate from the cutaneous inflammatory pathways for the direct dermatological relevance.

5.4. NPs specific mechanistic summary

Table 3. The dominant mechanistic actions of various NPs that included in this study.

Type of NPs	Dominant mechanistic actions	Penetration/reactivity actions from the included evidence basis
ZnO NPs	The dissolution of Zn^{2+} ion (pH-dependent, acidic-favoured) and involves in the photocatalytic ROS generation at UV-active surfaces.	The Order-of-magnitude increase in barrier-impaired vs intact skin [17].
TiO_2 NPs	The Photocatalytic ROS generation can be done (band-alignment-dependent, phase-dependent) though it having minimal dissolution capacity.	Comparison between the intact vs damaged skin in the included evidence [35].
Ag NPs	The Ag^+ ion release that leads to the oligodynamic membrane/enzyme disruption in the microbes that also called as morphology-dependent reactivity.	Ex vivo penetration demonstrated; shape-dependent deposition [42, 43].
Au NPs	The Chemically inert core that acts as primary physical/plasmonic and carrier behaviour rather than ion release.	Used constructively as a co-delivery vehicle [47].
CeO_2 NPs	The Reversible Ce^{3+}/Ce^{4+} redox cycling and catalytic neutralisation of reactive/toxic small molecules.	Reduces the penetration of a co-applied toxicant (organophosphate) [50].
SiO_2 NPs	Largely inert material that acts as a diffusion barrier/coating that restricts the ion release and ROS generation from a coated core.	Thickness-dependent reduction of ZnO from the core shell [51].

5.5. Mechanistic basis of NPs Comparison

The mechanistic contrast of NPs is summarized in Table 3. that provides the clearest explanation for the consistent comparative finding in Section 6. ZnO NPs penetration is strongly dependent on barrier status, whereas TiO_2 NPs penetration independent of it (Section 6.4, Figure 5). ZnO NPs crosses the skin primarily through dissolution into diffusible ions, the barrier impairment that disproportionately enhances its effective transport. By contrast, TiO_2 NPs remains intact as particulate material regardless of barrier condition that reflects the direct particle transport of similar magnitude in intact and damaged skin, as shown through the Franz-cell studies. This interpretation is mainly used for the extraction of data from the mechanistic reading, rather than as an additional independent finding beyond those reported in Sections 4 and 6.

6. QUANTITATIVE SYNTHESIS

6.1. Approaches for the Quantitative synthesis

This section proceeds on the NPs and their mechanistic synthesis in Sections 4–5, instead it presenting the cross-type of NPs for the quantitative comparisons derived exclusively from arm-level numeric outcome data (concentrations, percentages, effective/inhibitory values, fold-changes) extracted from full published texts (Section 2.5). Eight such comparisons were identified across the 39 included studies and that reported in Sections 6.2–6.10, each citing the source study, verified DOI, and exact values plotted. Where studies reported group means without variance, or significant differences without numeric values for one arm, this limitation is stated explicitly rather than supplemented with invented data (see Section 6.6, Figure 10b for an example). Section 6.11 provides a structured evidence-density map across the NPs types and outcome domains, and Section 6.12 consolidates all eight comparisons in a single reference table. There are three types of evidential basis are distinguished: (i) matched head-to-head comparisons (Sections 6.2–6.3, 6.7–6.8), where multiple NPs types were tested side-by-side within the same experiment; (ii) matched dose-/structure-response comparisons (Section 6.6), where numeric series across engineered material variables enable genuine response relationships and (iii) functionally comparable cross-study comparisons (Sections 6.4–6.5), where independent studies using sufficiently similar methodology that allow direct numeric comparison, highlighted clearly.

6.2. Antibacterial effects (Biosynthesised ZnO NPs vs TiO₂ NPs)

A single study that directly compared the antibacterial strength of green-synthesised ZnO NPs and TiO₂ NPs. Both of these NPs were made using the same *Calotropis procera* leaf-extract and tested against the same bacterial strains (*Staphylococcus aureus* and *Escherichia coli*). The study measured efficacy using the zone-of-inhibition [14]. In both strains, ZnO NPs produced larger inhibition zones in two bacterial species than TiO₂ NPs, that we conclude the ZnO NPs have greater antibacterial activity (Figure 3). The ZnO NPs that release the Zn²⁺ ions to disrupt the membrane and enzymes and also induce the ROS production to explicit its antibacterial effects [10].

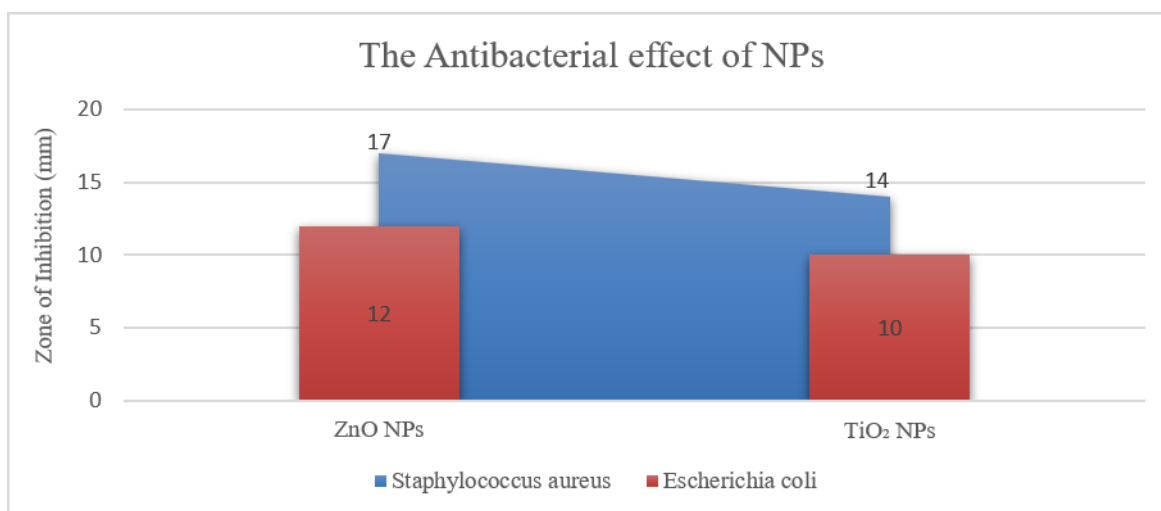


Figure 3. The Antibacterial effects of ZnO NPs and TiO₂ NPs based on their formation of Zone of Inhibition (mm)

6.3. Antioxidant activity (Biosynthesised ZnO NPs vs TiO₂ NPs)

The same study also measured the antioxidant activity through using the DPPH radical-scavenging assay [14]. In contrast to the antibacterial results, TiO₂ NPs that showed the slightly stronger radical-scavenging activity than ZnO NPs (Figure 4). Taken together, Sections 6.2–6.3 highlight a key point for cosmetic formulation that neither NPs type is uniformly superior. ZnO NPs demonstrates a clear advantage for antimicrobial applications, while TiO₂ NPs having a modest advantage for antioxidant activity from these (*Calotropis procera* leaf-extract) biosynthesised materials. However, these findings should not be generalized without caution to conventionally synthesised, differently sized, or differently coated ZnO/TiO₂ NPs (Section 4.8).

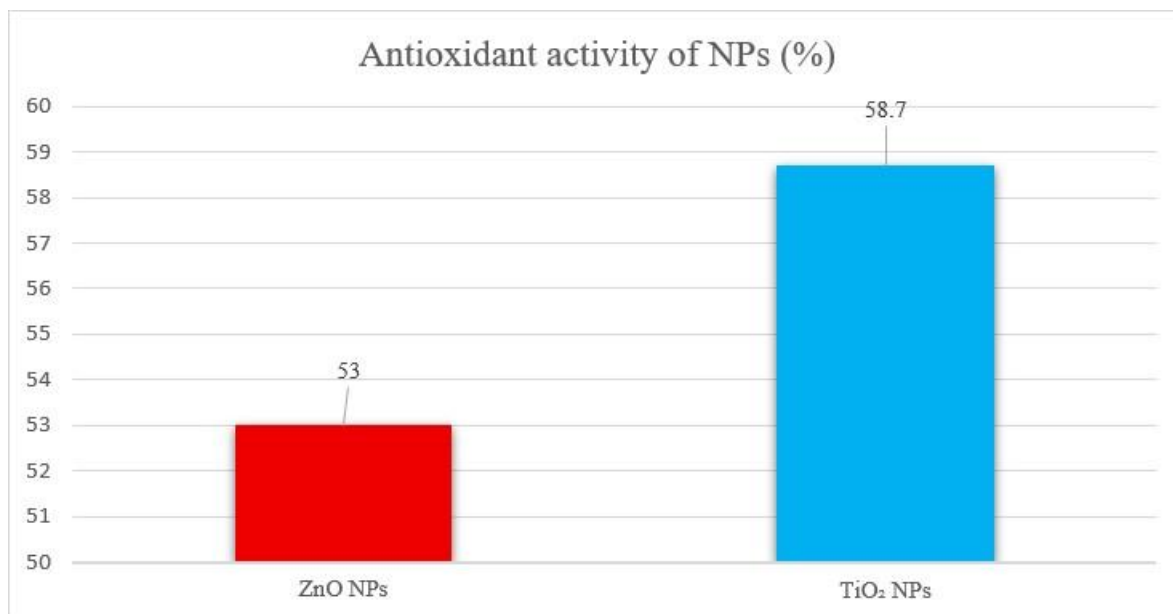


Figure 4. The Antioxidant activity of ZnO NPs and TiO₂ NPs (DPPH)

6.4. Barrier status dependent skin penetration (ZnO NPs vs TiO₂ NPs)

This comparison done on two independent Ex vivo human-skin studies for ZnO NPs [17] and TiO₂ NPs [35]. They used different vehicles (caprylic/capric triglyceride and artificial sweat for penetration of ZnO NPs and artificial sweat for penetration of TiO₂ NPs) and different barrier-impairment methods (occlusion protocol vs. needle abrasion). This evidence is functionally comparable rather than strictly matched. Along with the caution, the contrast is clear and mechanistically consistent (Figure 5 a); Section 5.5) that showed the ZnO NPs penetration was negligible under intact-skin conditions but increased sharply when the barrier impairment done. The concentration of ZnO NPs in the viable epidermis increasing upto 60–65-fold at 24 h and over 100-fold at 48 h that reflecting both barrier-status and time dependence.

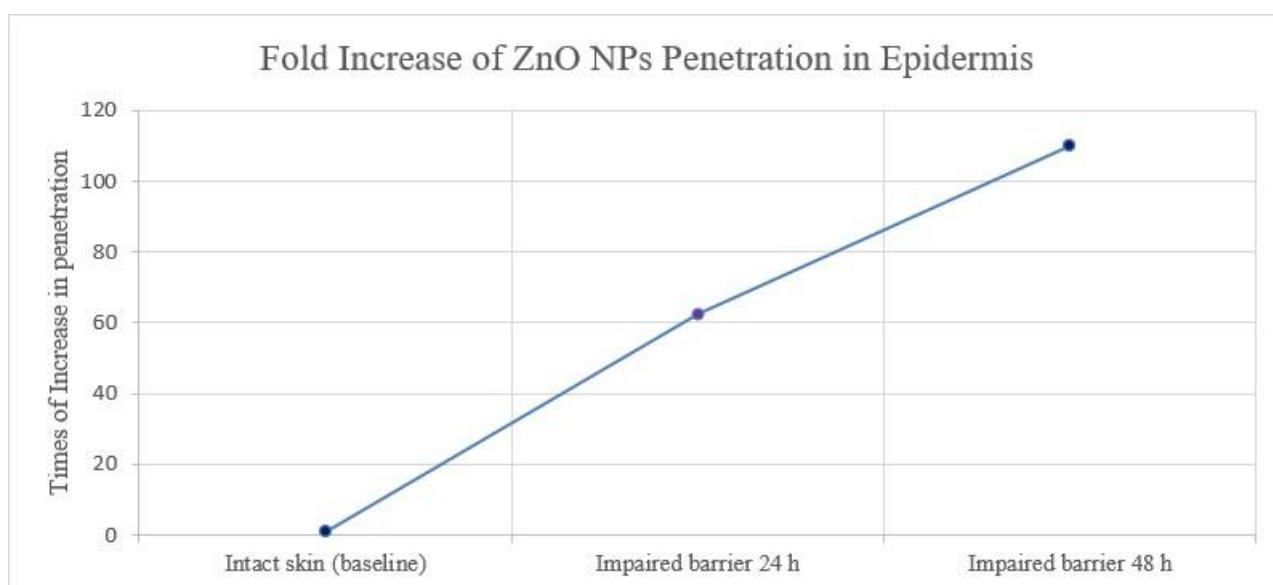


Figure 5 a). The Fold Increase of ZnO NPs in the epidermis (Ex vivo Human skin)

The study found that TiO₂ NPs deposition in the epidermis was similar between intact ($0.47 \pm 0.33 \mu\text{g}/\text{cm}^2$) and damaged ($0.53 \pm 0.26 \mu\text{g}/\text{cm}^2$) skin at 24 h, and no TiO₂ NPs was detected in the receiving (dermal-side) solution. Together, these findings support the mechanistic account in Section 5.5. ZnO NPs dissolution-mediated transport makes it highly sensitive when barrier

impaired, whereas TiO_2 NPs has non-dissolving transport that comparatively barrier-status-independent over the 24-hour window studied.

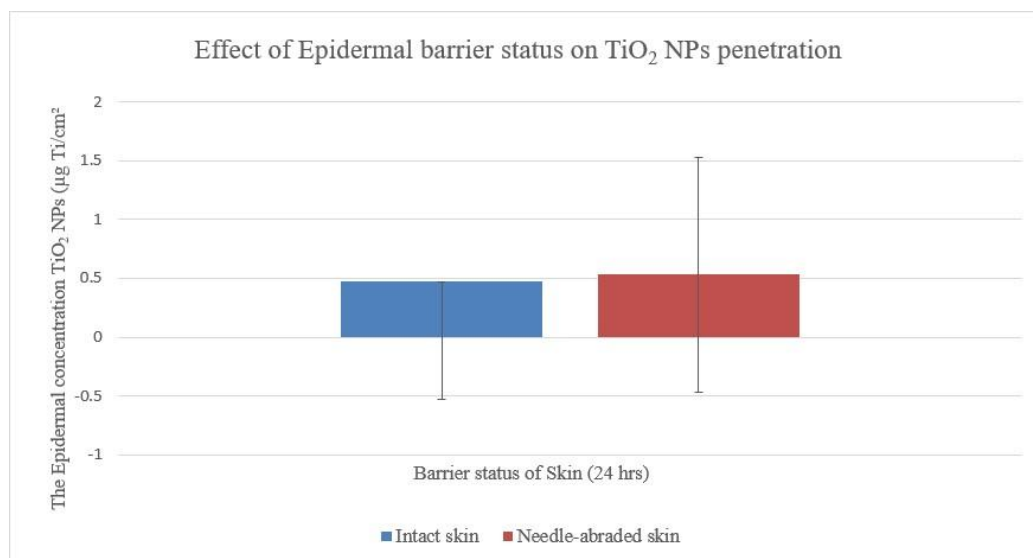


Figure 5 b). The TiO_2 NPs deposition in the Epidermis in different status of skin barrier.

6.5. Comparative cytotoxicity (ZnO NPs - Zn^{2+} ions vs TiO_2 NPs)

A further quantitative comparison done between Zn^{2+} - ion and TiO_2 NPs for their cytotoxicity thresholds in viable human epidermis as EC_{50} values in keratinocytes. The Zn^{2+} - ion threshold is consistently reported in the range of 21–31 $\mu\text{g/mL}$, based on Ex vivo human-skin studies with ^{67}Zn isotope tracing [15,18]. The studies of TiO_2 NPs as EC_{50} values, that done through expose the NPs for seven days into HaCaT cells and comparing the results of different assays. The results for the various assay 70.3 $\mu\text{g/mL}$ from MTT assay, 60.7 $\mu\text{g/mL}$ from propidium-iodide uptake assay, and 3.0 $\mu\text{g/mL}$ from AlamarBlue assay. The final result value unit is converted from molar concentration for direct comparability [35] (Figure 6). These values fall within a overlapping order of magnitude, but the TiO_2 NPs thresholds for the cytotoxicity can be differ sharply in different assays, thus showing that cytotoxicity cannot be fixed as single value. This variability is important when interpreting for the safety claims. Crucially, Zn^{2+} ion concentrations measured in human sunscreen-use studies (Section 4.1) remained well below the 21–31 $\mu\text{g/mL}$ threshold even after repeated application [15,18]. Thus, providing quantitative evidence that ZnO NPs - sunscreen use on intact skin does not reach cytotoxic levels in the viable epidermis.

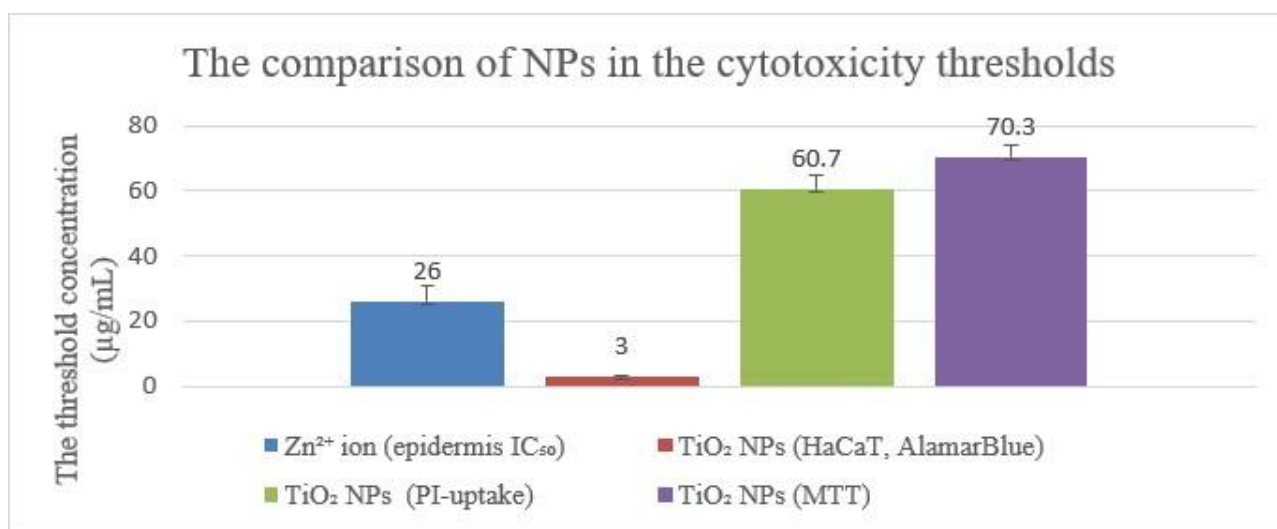


Figure 6. The comparison of ZnO NPs and TiO_2 in the In vitro cytotoxicity thresholds

6.6. Dosage ordered evidence of shell effects on NPs

A single study provides a matched, single-batch dataset that uses for the direct comparison of bare ZnO NPs with the ZnO NPs core coated by either a thin or thick SiO₂ shell, demonstrated in the human dermal fibroblast (HDFn) cells across four cytotoxicity endpoints [51]. This is the most comprehensive numeric dataset in the evidence base and reported (Figure 10). Across all results, the pattern was consistent and rely on dose-ordered. The bare ZnO NPs was the most cytotoxic (cell viability fell to ~3% at 50 µg/mL in 48 hr), thin SiO₂ coating offered little protection (~5% viability), while thick SiO₂ coating substantially reduced cytotoxicity (viability remained above 50% at 48 h, with 80% and 70% viability at 12 h and 24 h respectively). The LDH leakage in human dermal fibroblasts consistently demonstrated as a protective effect due to the surface modification of NPs. Bare ZnO NPs induced the highest membrane damage ($\approx 68 \pm 4\%$ vs. control), while thin SiO₂-coated ZnO showed moderately reduced leakage ($\approx 57 \pm 3\%$). In contrast, thick SiO₂ shells markedly attenuated cytotoxicity, with LDH release reduced to $26 \pm 7\%$. The same ordering applied to the oxidative stress in that thick-shell particles produced 30% less ROS when compared to control. Whereas bare ZnO NPs and thin-shell particles (SiO₂NPs – ZnO NPs) increased ROS by 97% and 80% than control respectively. The Lipid peroxidation followed the same pattern that with fold-increases of 6.0, 3.5, and 2.0 for bare ZnO NPs, thin coated, and thick coated (SiO₂) ZnO NPs respectively when compared with control. This matched dataset explains, with dose-ordered numeric evidence rather than categorical claims, the mechanistic point emphasized in Section 5.2. The surface engineering is a first-order, quantifiable determinant of cosmetic NPs cytotoxicity, with an impact of comparing to change the NPs core itself.

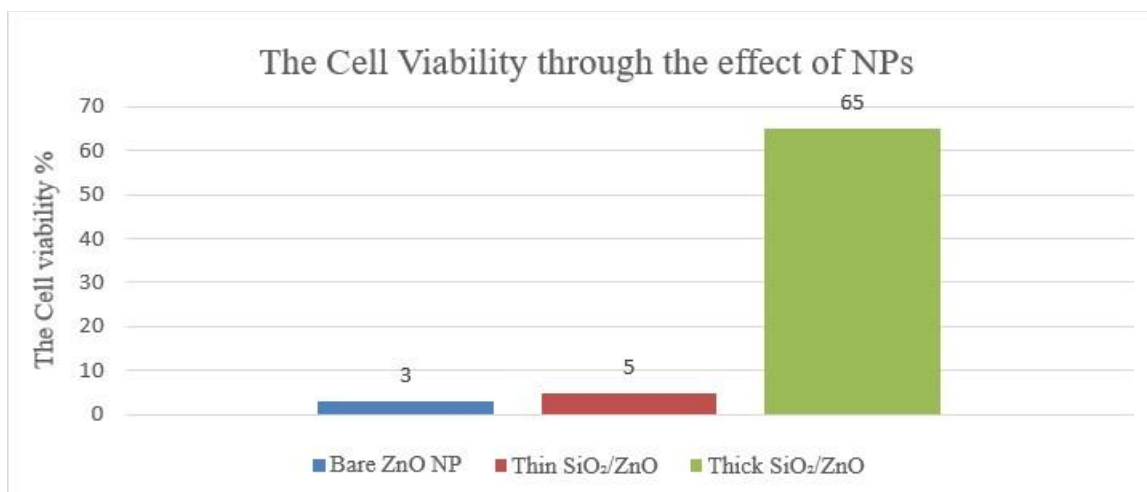


Figure 7. a) The Cell viability assessment through MTT assay across the ZnO NPs and Thin Thick SiO₂ NPs shell coated ZnO NPs

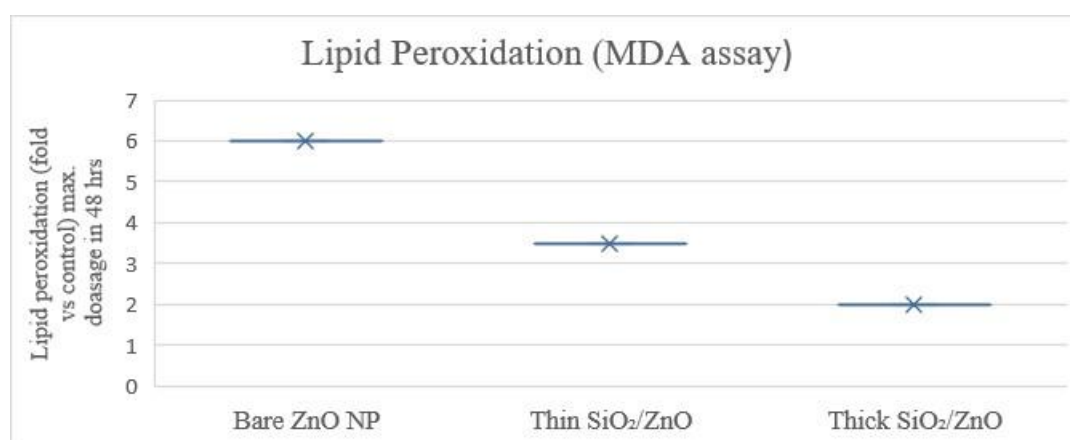


Figure 7. b) The Membrane damage (LDH leakage) effects of the ZnO NPs and Thin Thick SiO₂ NPs shell coated ZnO NPs

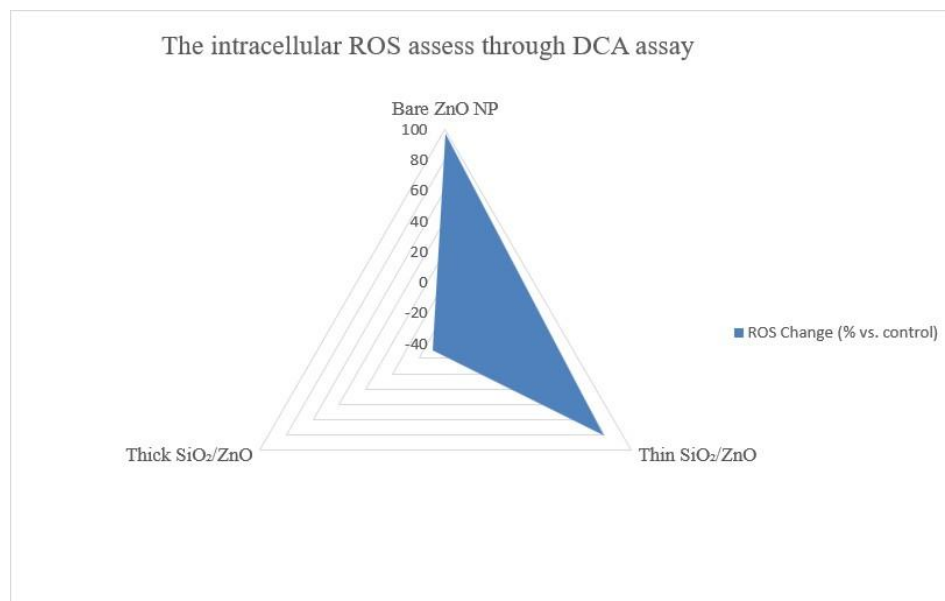


Figure 7. c) The Intracellular ROS response effects of the ZnO NPs and Thin Thick SiO₂ NPs shell coated ZnO NPs

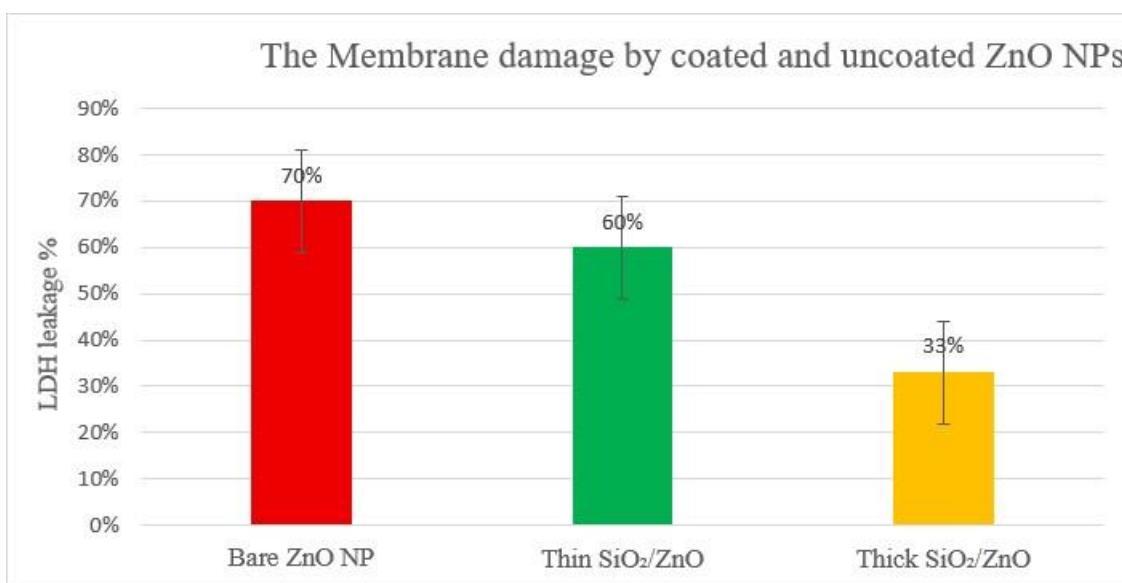


Figure 7. d) The Lipid peroxidation effects of the ZnO NPs and Thin Thick SiO₂ NPs shell coated ZnO NPs

6.7. Detection of NPs in the cosmetics products (TiO₂ NPs vs Au NPs)

A multi-technique analytical screening study (dynamic light scattering, single-particle ICP-MS, ICP-MS, and ICP-OES) applied a uniform protocol to a set of marketed cosmetic products to determine the definite TiO₂ NPs and Au NPs content [41] (Figure 8). This provided a matched, same-protocol, same-product-set comparison of real-world prevalence. TiO₂ NPs was detected in every sampled product such as sunscreen, anti-wrinkle day cream, lip balm protector, and toothpaste. In that one toothpaste product not labelled as that containing nanomaterial but it has measurable nanoscale of TiO₂ NPs. This makes a compliance issue with direct regulatory relevance (Section 1.3). In contrast, Au NPs were not detected in any product, consistent with the narrative synthesis in Section 4.4. The Au NPs role in the cosmetic remains on emerging and premium delivery applications rather than widespread marketed use at the time of sampling.

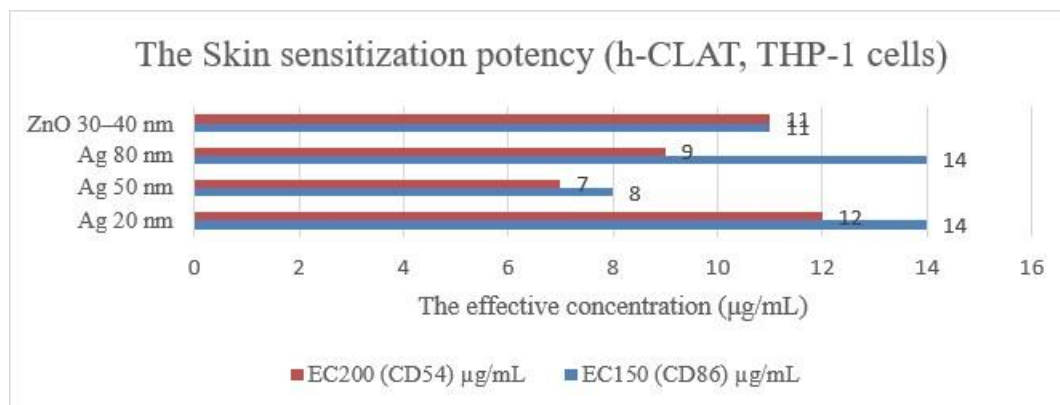


Figure 8. The Detection of TiO₂ NPs vs Au NPs in the various cosmetic products. (Au NPs not present in any product)

6.8. The sensitisation potency (Ag NPs (3 different particles size) vs ZnO NPs)

A human cell-line activation test (h-CLAT) an In vitro assay (OECD TG 442E) that used to assess chemical skin-sensitisation potential through CD86 and CD54 dendritic cell surrogate marker expression in THP-1-cells. This can be used to assessing the sensitizing potential of Ag NPs (20, 50, and 80 nm) and ZnO NPs under matched laboratory conditions [46]. All four materials were classified positive for sensitisation potential (EC150 for CD86, EC200 for CD54) (Figure 9), but their potency profiles differed. The 50 nm Ag NPs showed the lowest effective concentrations (EC150 = 8 µg/mL, EC200 = 7 µg/mL), though they were positive in only two of three runs. The 20 nm and 80 nm Ag NPs required higher concentrations (EC150 = 14 µg/mL for both). ZnO NPs required intermediate concentrations (EC150 = EC200 = 11 µg/mL) but were positive in all three runs. This indicating the most consistent sensitisation signal, even if not the most potent per unit concentration. The Ag NPs potency cannot assess monotonically with only particle size and also parallels the shape-dependence of Ag NPs for antimicrobial and cytotoxic effects that noted in Section 4.3 [43]. It supports the point that Ag NPs is not a single material for safety assessment purposes.

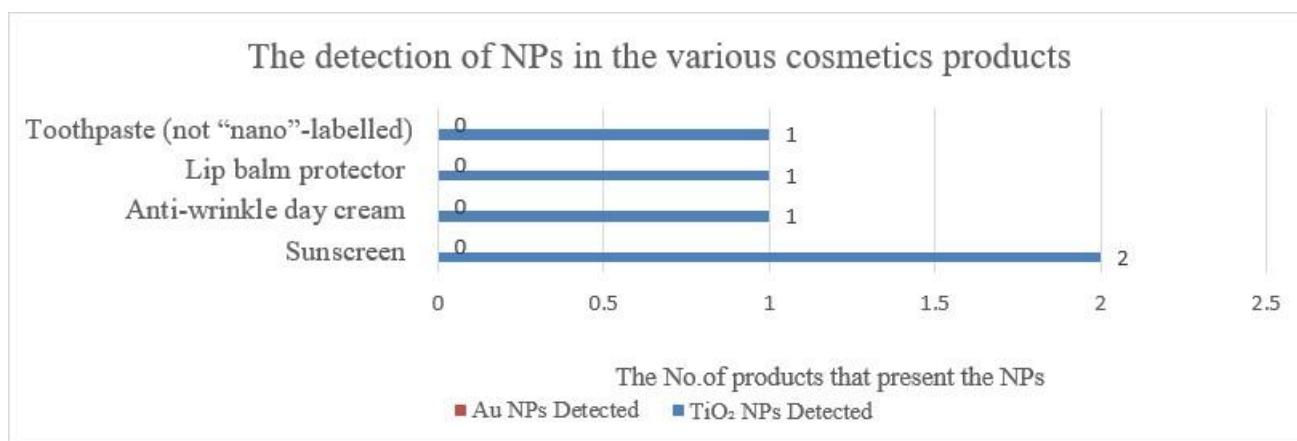


Figure 9. The skin sensitization potential assay (h-CLAT, THP-1 cells) as the effective concentration of ZnO NPs vs Ag NPs (20, 50, 80 nm).

6.9. The Co-exposure effects of ZnO NPs and TiO₂ NPs and their toxicity profile

The effects of ZnO NPs and TiO₂ NPs are often co-formulated in the sunscreens products and their combined toxicity is directly relevant to the cosmetic safety. The co-exposure study in HaCaT keratinocytes and a reconstructed human epidermis model (EpiSkin) found that ZnO NPs alone inhibited the cell proliferation and cause dose-dependent DNA damage. However, these effects were reduced when additionally, TiO₂ NPs were present in the same formulations (contain ZnO NPs and TiO₂ NPs). The Mechanistic analysis showed that TiO₂ NPs restricted cellular uptake of both aggregated and non-aggregated ZnO NPs and decreased intracellular Zn²⁺ ion release [39]. The interaction of these NPs was antagonistic, not additive or synergistic. The ZnO NPs alone reduced viability to below 60% at higher doses, while the co-exposure of ZnO NPs and TiO₂ NPs that maintained the viability above 80% under the same conditions. The key point remains that the co-formulation of ZnO NPs and TiO₂ NPs does

not simply combine two independent risks but produces a distinct, protective interaction profile.

6.10. The Functional protective role of CeO₂ NPs

This section focusses on the comparison of toxicity or detection results and also comparison of functional protective efficacy. A single study tested the incorporation of CeO₂ NPs into a topical barrier-cream formulation for its effect on skin penetration of a co-applied organophosphate toxicant (paraoxon), using Franz diffusion cells with a silicone-membrane surrogate model [50] (Figure 10). The Formulations containing CeO₂ NPs that reduced paraoxon penetration by a factor of 3–4 times when compared to the same formulation without CeO₂ NPs. Although this evidence is limited to one toxicant and one formulation type, this included because it represents the only functional (rather than purely toxicological) quantitative comparison in the evidence base. It highlights a distinct value plan for CeO₂ NPs relative to the other six nanoparticle types reviewed. It has a protective or detoxifying function, rather than UV filtration, antimicrobial action, or delivery.

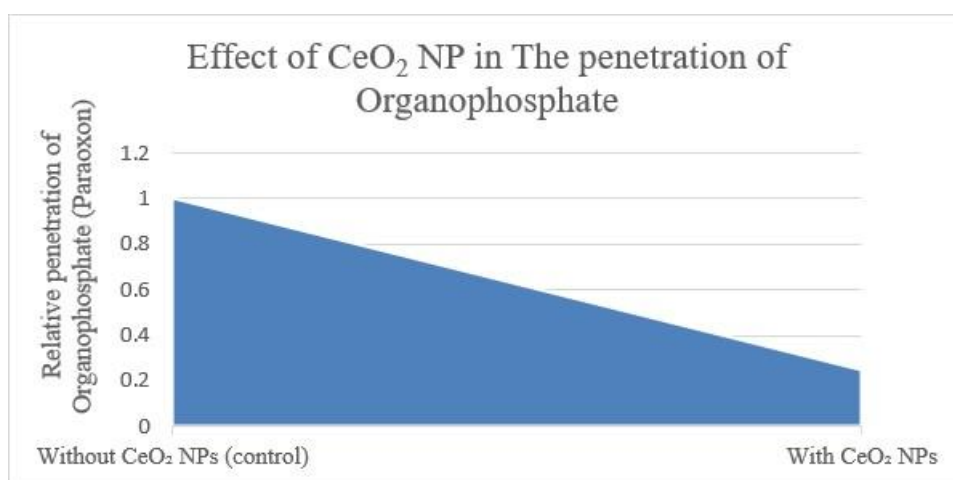


Figure 10. The functional protective efficiency of CeO₂ NPs in the penetration of Organophosphate (Paraaxon) Through Franz cell assay.

6.11. Evidence density map and Summary of Numeric output comparison of various NPs studies

Sections 6.2–6.10 present eight matched, structure-response, or functionally comparable numeric-outcome comparisons. While (Figure 11) positions these broader evidence base by mapping the NPs types against outcome domains across all 39 included studies. This evidence-density map highlights areas of depth (e.g., ZnO cytotoxicity and penetration) versus gaps (e.g., CeO₂, SiO₂, Al₂O₃) and also supporting the regulatory caution noted in Section 7.3. Then the Table 4 combines the eight quantitative comparisons, summarising comparison type, direction of findings, and references, providing a single reference point for the synthesis. Together, the map and summary table make transparency in both the evidential strengths and the limitations of the literature

Sect.	The comparison of NPs	Outcome metric)	(numeric	Comparison type	Direction of finding	Reference
6.2–6.3	ZnO NPs vs TiO ₂ NPs	Antibacterial ZOI (mm) and DPPH antioxidant (%)		Matched (same synthesis batch, same isolates)	ZnO NPs > TiO ₂ NPs antibacterial effect and TiO ₂ NPs > ZnO NPs antioxidant effect	[14]
6.4	ZnO NPs vs TiO ₂ NPs	Barrier-status-dependent penetration (fold vs. control; µg/cm ²)		Functionally comparable (independent studies, comparable design)	ZnO NPs markedly barrier-dependent (up to >100×) and TiO ₂ NPs largely barrier-independent	[17, 35]

6.5	Zn ²⁺ vs TiO ₂ NPs	In vitro cytotoxicity threshold (µg/mL)	Functionally comparable (independent studies)	Overlapping the order of magnitude (~3–31 µg/mL range across assays)	[15, 18, 35]
6.6	Bare ZnO NPs vs thin/thick SiO ₂ NPs/ZnO NPs	Viability (%), LDH (%), ROS (%), lipid peroxidation (fold) — 4 endpoints	Matched dose–/structure–response (single study, same batch)	Coating thickness that inversely correlates with cytotoxicity on all 4 endpoints.	[51]
6.7	TiO ₂ NPs vs Au NPs	Detection prevalence in marketed products (n products)	Matched (same analytical protocol, same product set)	TiO ₂ NPs detected more frequently than Au NPs in cosmetic products	[41]
6.8	Ag NPs (20/50/80 nm) vs ZnO NPs	Skin-sensitisation potency, EC ₁₅₀ /EC ₂₀₀ (µg/mL)	Matched (same h-CLAT assay, same laboratory)	All 4 materials give positive from that Ag NPs in 50 nm most potent by EC, ZnO NPs most consistent (3/3 runs)	[46]
6.9	ZnO NPs + TiO ₂ NPs (combined)	Co-exposure cytotoxicity/DNA damage (directional)	Matched (same cell/tissue model)	Antagonistic effect that TiO ₂ NPs reduced ZnO NPs-induced toxicity	[39]
6.10	CeO ₂ NPs	Organophosphate skin-penetration reduction (fold)	Single-study functional comparison	3–4-fold reduction with CeO ₂ NPs incorporation	[50]

Table 4. The summary of Eight numeric comparison of different NPs types.

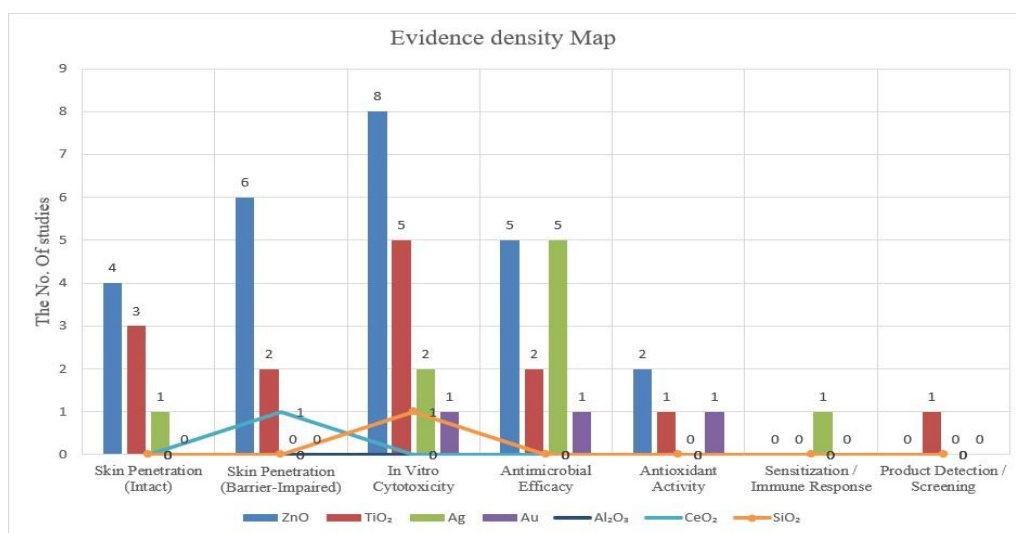


Figure 11. The Evidence density map that showing the No.of studies (Primary) included based on the NPs type and result / outcome domain.

7. DISCUSSION

7.1. Key Findings

This review aimed for the quantitative comparison of metal and metal-oxide NPs in cosmetic and dermal-exposure backgrounds. Three key findings emerge: (1) the evidence base is heavily concentrated on ZnO NPs and TiO₂ NPs, with limited human In vivo data. (2) The barrier integrity consistently shapes penetration results, with ZnO NPs showing the strong barrier-status dependence while TiO₂ NPs does not depends on the barrier status. (3) The direct head-to-head comparisons of studies that reveal there is no uniformly superior material. In that ZnO NPs is stronger in antibacterial efficacy, TiO₂ NPs marginally stronger in antioxidant capacity, and their co-formulation produces an antagonistic rather than additive in the toxicity profile. Together, these findings highlight the importance of matched, functionally comparable extraction for the mechanistic contrast revealing and that not obtained from the narrative synthesis alone.

7.2. Functional specific Comparison of Cosmetic NPs

The Sections 4 and 6 support a function-specific role rather than universal ranking of NPs types. For UV filtration, both ZnO NPs and TiO₂ NPs that remain well-evidenced, though ZnO NPs shows greater barrier-status sensitivity while TiO₂ is more consistent in a distinction relevant to compromised-skin populations. For antimicrobial applications, Ag NPs holds an advantage and that strengthened by morphology-dependent cytotoxicity and deposition effects. For antioxidant activities, TiO₂ NPs having marginal DPPH advantage over ZnO NPs from a single study. While CeO₂ NPs shows the most direct redox-based protective mechanism than other NPs type. For delivery and antifading uses, Au NPs inertness and co-delivery utility position it favourably, though the dermal-safety evidence remains comparatively thin. Together, these findings highlighten that NPs utility is context-specific, with distinct strengths across functional domains rather than a single hierarchy of safety or efficacy.

7.3. Formulation and Regulatory implications of NPs evidence

For risk assessment and product-formulation purposes, the concentration of evidence around ZnO NPs / TiO₂ NPs in the sunscreen-type exposure situations. This means that the barrier-status-dependent penetration pattern identified here so that considered as well-established specifically for those two NPs types. The extrapolation to Al₂O₃ NPs, SiO₂ NPs, and CeO₂ NPs should be treated as provisional pending in a larger primary evidence base. It has a consistent with an evidence gap rather than demonstrated maltreatment framing used by recent regulatory-facing reviews of long-term nanomaterial exposure [6, 13]. The product-detection finding in Section 6.7 — nanoscale TiO₂ NPs present in a toothpaste product and that not labelled as containing nanomaterial [41] It is an existing, actionable illustration of the practical importance of the EU nano-labelling requirement discussed in Section 1.3, independent of whatever the underlying safety profile of that TiO₂ NPs material. The antagonistic ZnO NPs /TiO₂ NPs co-exposure finding (Section 6.9) similarly has direct formulation relevance: It cautions against assuming that a mineral-sunscreen blend's safety profile is a simple sum of its two components' individually and characterised their profiles, in either direction.

7.4. The Methodological comparisons with prior reviews

Prior reviews in this field have generally taken one of two approaches. The narrative synthesis that describes about the mechanisms and safety in a qualitative manner without reproducible search protocols, and systematic reviews that limited to bibliographic description because abstract-level records rarely provide pool able arm-level data. The present review advances methodologically by restricting quantitative claims to matched or functionally comparable head-to-head comparisons genuinely present in the included literature (Section 6). Rather than abandoning quantitative synthesis or fabricating pooled statistics unsupported by the data. It also demonstrates that defensible comparative synthesis is achievable, while explicitly noting that a formal meta-analysis (pooled effect sizes, forest plots, heterogeneity statistics) would still require additional full-text arm-level data extraction beyond the scope of this review.

8. REVIEW LIMITATIONS

- ☐ **Database Scope:** Only PubMed and Scopus were searched. Other databases and grey literature were excluded, so some eligible studies may not have been captured.
- ☐ **Risk-of-Bias Assessment:** No formal, tool-based risk-of-bias assessment was done. The Study quality was not systematically assessed, which is a recognised limitation and recommended for the next action (Section 9).

- **Quantitative Approach:** This review is not a pooled statistical meta-analysis. The 39 included studies were too heterogeneous for defensible effect-size pooling. Instead, Section 6 maximises the genuine matched or functionally comparable quantitative content, along with this dissimilarity, maintained the clear opinion throughout the review.
- **Reviewer Process:** All stages of study selection, data extraction, and comparison identification were conducted by a single reviewer.
- **Evidence-Density Map:** Figure 11 is a bibliometric tool that counts contributing studies per NPs-type/outcome-domain cell. It does not encode the direction or magnitude of the effect and that should not be interpreted.
- **Comparisons Across Independent Studies:** Functional (non-matched) comparisons in Sections 6.4–6.5 carries additional uncertainty. While methodologically similar comparisons enough to be informative, they are less rigorous than strictly matched, single-study comparisons (Sections 6.2–6.3, 6.7–6.8).
- **Thin Evidence for Certain NPs:** Conclusions for CeO₂, SiO₂, and Al₂O₃ rest on extremely limited evidence: one study each for CeO₂ and SiO₂, and none for Al₂O₃.

9. CONCLUSIONS

Following PRISMA 2020 guidelines, a two-stage search of PubMed and Scopus identified 39 eligible primary studies and clinical/case reports on seven cosmetic metal/metal-oxide NPs, with evidence concentrated on ZnO and TiO₂ and dominated by In vitro and animal models. The review's central contribution is a genuine quantitative comparative synthesis: eight matched, structure-response, or functionally comparable numeric-outcome comparisons were extracted from full texts, verified against original publications, and presented in dedicated figures (Sections 6.2–6.10), supported by an evidence-density map (Section 6.11). The clearest quantitative pattern is ZnO's sharply barrier-status-dependent penetration (up to two orders of magnitude higher in impaired skin) versus TiO₂'s barrier-independent profile that reflecting their distinct dissolution-mediated versus particulate transport mechanisms. The evidence for Al₂O₃ NPs, SiO₂ NPs, and CeO₂ NPs remains thin, and conclusions for these types are provisional. A full statistical meta-analysis of ZnO/TiO₂ NPs penetration and safety outcomes is a next logical step and requiring harmonised arm-level data extraction from directly comparable studies.

Authors contributions

Vigneshwaran G: Investigation, writing - original draft, methodology, data curation. Balavinayagamani Ganapathy: Conceptualization, writing – review & editing, supervision, and validation.

Ethical Statement

Not applicable.

Use of Artificial Intelligence (AI) Tools

This is our OWN work. We used information from a source in order to create the table/graph, and the sources are cited. The authors confirm that they used artificial intelligence (AI) tool for language checking of the manuscript after the preparation of the article.

Declaration of competing interest

The authors declare that they have no known competing interests.

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(1-13 background review references) (14-52 primary study references)

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